LIPPINCOTT WILLIAMS & WILKINS

AIDS
Official Journal of the International AIDS Society

Volume 14(7) 5 May 2000 pp 821-826

Effect of chemokine receptor gene polymorphisms on the response to potent antiretroviral therapy

[Clinical]

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Received: 20 October 1999;
revised: 10 December 1999; accepted: 22 December 1999.

Sponsorship: This work was supported by grants AI 27670, AI 38858, and AI 36214 (Center for AIDS Research) and grant AI 29164 from the National Institutes of Health; by the Research Center for AIDS and HIV Infection of the San Diego Veterans Affairs Medical Center; and by Intramural Research Programs of the National Cancer Institute and the National Institute of Allergy and Infectious Diseases.

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Outline

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Abstract

Background: Both the natural history of HIV infection and the response to antiretroviral therapy are heterogeneous. Polymorphisms in chemokine receptor genes modulate the natural history of HIV-1 infection. In comparison with subjects with other genotypes, the prognosis for HIV-1-infected *CCR5*-[DELTA]*32* heterozygotes is more favorable and that for *CCR5* promoter allele *59029A* homozygotes is less favorable.

Methods: HIV-1-infected adults with a CD4+ lymphocyte count >= 200 cells × 10^6/l and a plasma HIV RNA level >= 1000 copies/ml were treated with indinavir, zidovudine and lamivudine for 6 months. HIV RNA levels were measured at 4-week intervals. Genotyping for chemokine receptor gene polymorphisms (*CCR5-[DELTA]32*, *CCR5 59029A/G*, *CCR2-64I*) was performed. We examined whether the time to first HIV RNA < 200 copies/ml, frequency of viral suppression failure (HIV RNA >= 200 copies/ml between weeks 16 and 28 of therapy), or reduction from the pre-treatment HIV RNA level differed by genotype.

Results: Time to first HIV RNA < 200 copies/ml was not predicted by genotype. Among 272 Caucasian patients, viral suppression failure was more common among patients with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype (28%) than among all other subjects combined (relative risk, 2.0;$P = 0.06$). After 24 weeks of therapy, genotype groups differed in the reduction of the HIV RNA level from baseline ($P = 0.02$); patients with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype had a mean reduction of 2.12 $\log_{10}$ copies/ml compared to 2.64 $\log_{10}$ copies/ml among all other groups combined.

Conclusion: Polymorphisms in chemokine receptor genes may explain some of the heterogeneity in sustaining viral suppression observed among patients receiving potent antiretroviral therapy.

Introduction

CC-chemokine receptor 5 (CCR5) is the major coreceptor for macrophage-tropic HIV-1 strains. Homozygosity for a 32 base pair deletion (*[DELTA]32*) of the *CCR5* gene provides strong relative protection against HIV-1 infection [1–5], and HIV-1-infected *CCR5-[DELTA]32* heterozygotes have a more favorable natural history than do people with two wild type alleles [3,4,6]. The *CCR5-[DELTA]32* allele is much more common in Caucasians than in other racial groups.

Variants of other chemokine receptor genes also may alter the course of HIV-1 infection. Heterozygosity or homozygosity for the *CCR2-64I* allele of the minor HIV coreceptor CCR2b has been associated with better prognosis [6,7]; and homozygosity for *CCR5* promoter alleles *59029 A*[8] and *P1*[9] has been associated with worse prognosis. The *59029 A* and *P1* alleles

appear to define the same haplotype [10]. Homozygosity for the *SDF-1 3'A* allele of the gene which codes for SDF-1 (the chemokine ligand of CXCR4) also has been associated with better prognosis [11], but those data are less consistent [10,12]. The mechanisms by which genetic polymorphisms alter HIV-1 disease progression is not completely known, but the *CCR5-[DELTA]32* and *CCR2-64I* alleles are associated with lower levels of viremia during early chronic HIV-1 infection [6], which is a strong determinant of prognosis [13,14].

As genetic markers predict the natural history of HIV-1 infection and the response to antiretroviral therapy is heterogeneous, it is possible that treatment response is genetically determined. We, therefore, hypothesized that patients with the *CCR5-[DELTA]32* and *CCR2-64I* alleles would have a better response to potent antiretroviral therapy and patients with the *CCR5 59029 A/ A* genotype who lacked a protective allele would have a less favorable response. We examined these hypotheses among subjects who received a uniform regimen of antiretroviral therapy in the AIDS Clinical Trial Group 343 Study (ACTG 343) [15].

Methods

Subjects

The ACTG 343 study was designed to determine if patients with low viral levels after a 6-month induction with triple-drug combination therapy could maintain viral suppression with lesser therapy [15]. Enrollment in the ACTG 343 Study was limited to HIV-1-infected adults with a CD4+ lymphocyte count >= 200 cells × 10^6/l and a plasma HIV RNA level >= 1000 copies/ml. Patients were ineligible if they had received HIV protease-inhibitor therapy for more than 2 weeks; received lamivudine or abacavir therapy at any time; or had known intolerance of zidovudine. All enrollees gave written informed consent. In the induction phase, subjects received open-label treatment with indinavir (Crixivan; Merck, West Point, Pennsylvania, USA; 800 mg every 8 h), lamivudine (Epivir; Glaxo Wellcome, Research Triangle Park, North Carolina, USA; 150 mg twice daily), and zidovudine (Retrovir; Glaxo Wellcome; 300 mg twice daily). For subjects who had adverse reactions to zidovudine during the study, a reduction in the dose to 100 mg three times daily was allowed. Zidovudine-intolerant subjects were permitted to substitute stavudine (Zerit; Bristol-Myers Squibb, Princeton, New Jersey, USA; 40 mg twice daily) for zidovudine. Subjects who could not tolerate full-dose stavudine, lamivudine, or indinavir were withdrawn from the trial. Assessment of drug toxicity, routine laboratory monitoring, and determination of T-lymphocyte subtypes by flow cytometry were performed at intervals of 4 to 8 weeks throughout the study. Plasma for HIV RNA determination was obtained every 4 weeks, stored at -70°C, and assayed after 24 weeks of induction therapy.

Subjects whose HIV RNA level remained < 200 copies/ml after completion of induction were randomized to one of three maintenance regimens (indinavir, zidovudine and lamivudine; zidovudine and lamivudine; indinavir alone). Because a review showed significant differences in suppression of HIV RNA among the three maintenance therapies, the study was terminated in its original form 5 months after the first subject enrolled into the maintenance phase. The analysis in this report is limited to data obtained during the induction period of the trial.

Laboratory measurements

Levels of HIV RNA were measured at the Johns Hopkins Medical Laboratory with the ultra-sensitive version of the Roche Amplicor HIV Assay (Roche Molecular Systems, Alameda, California, USA). A pre-treatment plasma sample was later analyzed for viral mutations conferring resistance to zidovudine and lamivudine by the line-probe reverse-transcriptase assay

[16].

A commercial kit (QIAamp DNA Blood Kit; QIAGEN Inc., Valencia, California, USA) was used to extract DNA from archived peripheral blood lymphocytes. Genotype for the *CCR5-[DELTA]32* and *SDF-1 3'A* alleles was determined by polymerase chain reaction amplification of DNA followed by polyacrylamide gel analysis for *CCR5-[DELTA]32* or restriction fragment length polymorphism (RFLP) analysis for *SDF-1 3'A. CCR2-64I* genotype was determined by a rapid single step allelic discrimination assay utilizing the ABI Prism 7700 Sequence Detector. (Chiuchin Yuan, manuscript submitted) *CCR5-59029* genotype was determined by RFLP analysis as previously described [8]. For a few subjects, genotype for one or more alleles could not be determined due to an inadequate specimen.

Data analysis

The rate of early viral clearance was determined by constructing a Kaplan–Meier plot [17] of the time from the initiation of triple therapy to that of the first HIV RNA level < 200 copies/ml. A separate Kaplan–Meier analysis used the first HIV RNA level < 50 copies/ml as the endpoint. The log-rank test was utilized to calculate the overall *P*-value [17]. Differences in HIV RNA levels among the genotypes at different time points were evaluated by analysis of variance performed in Advanced SPSS (SPSS Inc, Chicago, Illinois, USA). HIV RNA data for week 28 is not presented because those data are affected by selection bias – the only patients who had a week 28 measurement were those who met the ACTG 343 suppression criteria based on all HIV RNA measurements through week 24.

We examined the failure to suppress viral replication during the induction (triple therapy) phase of the study, as this part of ACTG 343 closely simulates the current standard for antiretroviral therapy. Patients with any HIV RNA level measurement >= 200 copies/ml during weeks 16 to 28 of the induction phase were considered treatment failures [15]. Because the frequency of the *CCR5-[DELTA]32* allele varies markedly by race, we restricted the primary analysis to white, non-Hispanic subjects. Analyses were also performed in which we controlled for race, CD4+ lymphocyte count, HIV RNA level, and zidovudine resistance in multivariate logistic regression models [18]. Zidovudine resistance was defined as a mutation at codon 215 (or codon 41 if viral genotype for codon 215 was unavailable for technical reasons) in a pre-treatment plasma sample.

Results

Subjects

We obtained complete genotype information for 504 of the 509 subjects who enrolled in ACTG 343, including 307 of the 309 white, non-Hispanic subjects who were the primary focus of our analysis. These 307 subjects were predominately male (88%), with a median age of 37 years. Fifty-six percent had previously been treated with zidovudine. The median CD4+ lymphocyte count was 445 cells × 10^6/l and the median HIV RNA level was 4.09 $\log_{10}$ copies/ml.

Allele frequencies and linkage disequilibrium

Allele frequencies among the white non-Hispanic subjects were consistent with previous reports (*CCR5-[DELTA]32*, 12.7%;*CCR2-64I*, 9.1%;*CCR5 59029-A*, 55.2%). As expected, there were strong linkage disequilibria between the *CCR5-[DELTA]32*, *CCR2-64I*, and *CCR5-59029-A* alleles (data not shown). Patients with the *CCR5-[DELTA]32* allele were less likely to also

have the *CCR2-64I* allele and vice versa. Those with the *CCR5 59029-A* allele were more likely to have the *CCR5-[DELTA]32* allele and the *CCR2-64I* allele.

Time to initial viral suppression

HIV RNA levels from blood specimens collected before the initiation of triple therapy (baseline HIV RNA) did not differ significantly by genotype (Table 1). We found no evidence that host genotype predicted the time from the initiation of triple therapy to the first HIV RNA level < 200 copies/ml ($P = 0.69$, log-rank test) or to the first HIV RNA level < 50 copies/ml ($P = 0.45$, log-rank test; Kaplan–Meier plots not presented). Consistent with these findings, HIV RNA levels at weeks 4 to 12 did not vary significantly by genotype (data not presented) and genotype failed to predict the changes in HIV RNA levels that occurred between baseline and these early time-points. The data on the HIV RNA difference between baseline and week 8 are presented in Table 1.

Table 1. The proportion of patients who failed to maintain suppression of the HIV RNA level below 200 copies/ml during weeks 16–28 of treatment with potent antiretroviral therapy, mean baseline HIV RNA (log_{10} copies/ml), and mean difference from baseline HIV RNA, by host genotype.

Genotype			Failure rate	Mean baseline	Mean difference from baseline HIV RNA (SE)		
CCR5-Δ32	*CCR2-64I*	CCR5-59029	(%)	HIV RNA (SE)	Week 8	Week 16	Week 24*
+/+	+/+	A/A	7/25 (28)	3.89 (0.13)	−2.20 (0.19)	−2.29 (0.23)	−2.12 (0.26)
+/+	+/−	A/G	12/90 (13)	4.13 (0.06)	−2.22 (0.06)	−2.59 (0.09)	−2.71 (0.09)
+/+	−/−	G/G	8/50 (16)	3.95 (0.09)	−2.21 (0.09)	−2.44 (0.11)	−2.63 (0.12)
+/Δ32	−/−	A/A or A/G	7/62 (11)	3.96 (0.09)	−2.06 (0.09)	−2.51 (0.10)	−2.57 (0.12)
+/+	+/64I or 64I/64I	A/A or A/G	7/40 (18)	4.13 (0.11)	−2.11 (0.09)	−2.49 (0.17)	−2.77 (0.14)
+/Δ32	+/64	A/A	2/5 (40)	3.79 (0.59)	−1.84 (0.22)	−1.70 (0.49)	−1.73 (0.34)
Total			43/272 (16)	4.03 (0.04)	−2.16 (0.04)	−2.48 (0.05)	−2.60 (0.06)

SE, standard error of the mean; * $P = 0.02$, analysis of variance.

Table 1. The proportion of patients who failed to maintain suppression of the HIV RNA level below 200 copies/ml during weeks 16–28 of treatment with potent antiretroviral therapy, mean baseline HIV RNA (log_{10} copies/ml), and mean difference from baseline HIV RNA, by host genotype. SE, standard error of the mean; *$P = 0.02$, analysis of variance.

Suppression failures

We examined viral suppression failure (HIV RNA level >= 200 copies/ml at any time during weeks 16–28 of therapy) among the 272 white, non-Hispanic patients who had not withdrawn from the study before week 16 (Table 1). Patients with the *CCR5 +/+ | CCR2+/+ | CCR5-59029* A/A genotype were 2.5-fold more likely to be suppression failures than *CCR5-[DELTA]32* heterozygotes (excluding five subjects who were heterozygous for both *CCR5-[DELTA]32* and *CCR2-64I*;$P = 0.06$) and two-fold more likely to be suppression failures than all other subjects combined ($P = 0.06$). When the five subjects who were heterozygous for both *CCR5-[DELTA]32* and *CCR2-64I* were included with the other *CCR5-[DELTA]32* heterozygotes, the *CCR5 +/+ | CCR2+/+ | CCR5-59029* A/A subjects were 2.1-fold more likely to have failed suppression of HIV-1 compared to *CCR5 +/[DELTA]32* subjects ($P = 0.10$). Similar findings resulted when the 35 subjects who withdrew before week 16 were classified as suppression failures or when we assumed that the suppression failure rate in these 35 subjects was the same as that of patients who did not withdraw (data not shown).

The genotypic differences in viral suppression were not explained by differences in CD4+ lymphocyte or HIV RNA measurements at study entry. In a multivariate logistic regression model, the strength of the effect was similar when these variables were considered (adjusted

odds ratio for *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A compared to *CCR5-[DELTA]32* heterozygotes, 2.5;$P = 0.10$). We observed consistent genotypic differences for viral suppression when we included baseline zidovudine resistance in the model (adjusted odds ratio, 3.4;$P = 0.06$).

There were 107 black non-Hispanic subjects, 48 Hispanic subjects and 14 subjects of another or unknown race who had not withdrawn by week 16. Among these subjects, suppression failure occurred in three of seven (42%) of those with +/+, +/+, A/A genotype compared to 54 of 162 (33%) of patients with other genotypes. Similar overall genotypic differences for viral suppression were observed when data from subjects of all races were included in an analysis that adjusted for race (adjusted odds ratio, 2.5;$P = 0.08$).

As another measure of viral suppression failure, we compared the HIV RNA level measurements at weeks 16, 20 and 24 with those obtained at baseline among the white, non-Hispanic patients. There were no significant differences at weeks 16 or 20, but patients with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype generally had the poorest response to therapy. The genotype groups differed significantly amongst themselves in the change in RNA at week 24 compared to baseline (Fig. 1, $P = 0.02$, one-way analysis of variance considering all possible haplotypes); patients with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype had a mean reduction from baseline of 2.12 $\log_{10}$ copies/ml compared with 2.64 $\log_{10}$ copies/ml among all other groups combined.

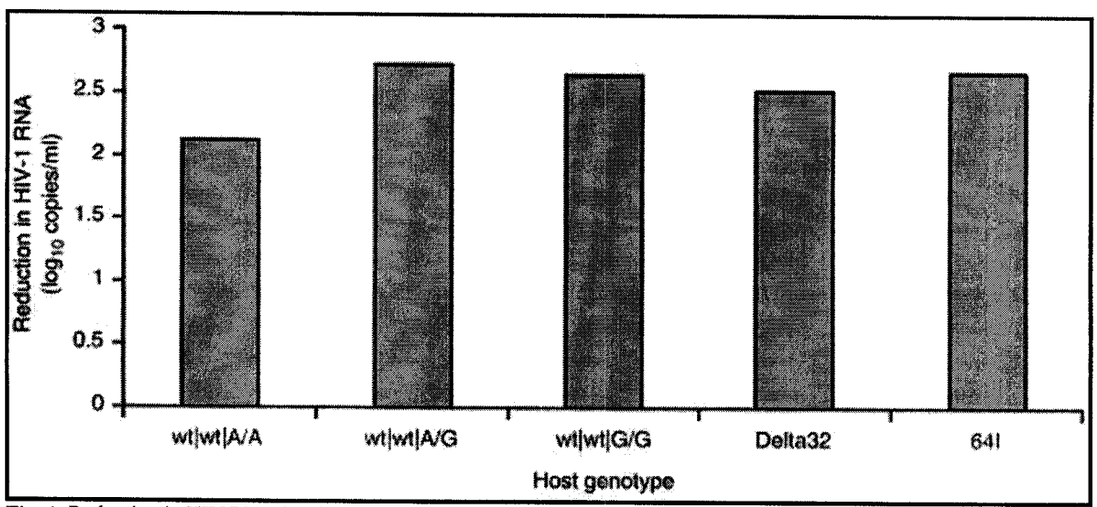

Fig. 1. Reduction in HIV RNA level after 24 weeks of potent antiretroviral therapy, by host genotype. X-axis labels refer to the *CCR5-[DELTA]32*, *CCR2-64I* and *CCR5-59029* polymorphisms, respectively (wt, homozygous wildtype; delta 32, heterozygous for the *CCR5-[DELTA]32* allele regardless of *CCR5-59029* genotype; 64I, heterozygous or homozygous for the *CCR2-64I* allele regardless of *CCR5-59029* genotype). Data from five subjects who were heterozygous for both the *CCR5-[DELTA]32* allele and the *CCR2-64I* allele are included with both the delta32 and the 64I groups.

SDF-1 polymorphism

In contrast to CCR5 polymorphisms, homozygosity for the *SDF-1 3'A* polymorphism was not associated with differences in therapeutic response. Comparing the homozygotes to the other subjects, initial viral suppression did not differ by genotype (data not presented). Among white, non-Hispanic subjects, the viral suppression failure frequency was slightly higher among homozygotes (five of 17; 29%) compared with other subjects (73 of 290; 25%). Similar results

were obtained when members of all racial groups were considered (data not presented).

Discussion

In this study of HIV-1-infected adults who were treated with indinavir, zidovudine and lamivudine, patients with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype were less likely to sustain viral suppression for 6 months than were patients with other genotypes. A second measure of treatment failure yielded a similar result – after 24 weeks of treatment, subjects with the *CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A genotype had the least reduction in the plasma HIV RNA level in comparison with the baseline value. These results are consistent with recent epidemiological studies of host genotype and HIV disease progression [8,9]. Our findings suggest that polymorphisms in the *CCR5* gene may explain some of the heterogeneity in viral suppression that has been observed among patients receiving potent antiretroviral therapy. Our study could not examine possible mechanisms for this effect, but these results could reflect genetically determined differences in expression of the major HIV-1 coreceptor CCR5. Previous studies suggest that such differences may underlie at least some of the observed variability in the natural history of HIV-1 infection [8,19,20].

Little evidence that host genotype affects the rate of early viral clearance was found, but that analysis was limited because HIV RNA levels were measured every 4 weeks in the ACTG 343 study. Monthly measurements may have been inadequate to detect genotypic differences in early viral clearance, most of which occurs within the first 2 weeks of potent antiretroviral therapy [21]. Alternatively, host genotype may have little effect on initial viral clearance, but may be important in maintaining suppression once low levels of replication are achieved.

Although modest genotypic differences in HIV RNA levels measured during early chronic infection have been reported in other studies [6], we found no statistically significant differences in baseline HIV RNA values among subjects with different genotypes. However, our study was not well situated to examine this question because ACTG 343 subjects were at an intermediate stage of infection at enrollment and many had received previous antiretroviral therapy. We were also limited in our ability to determine whether the genotypic effects we observed among white, non-Hispanic subjects were present in subjects of other racial/ethnic groups, because fewer subjects from these groups were enrolled in the ACTG 343 study.

The main difference in therapeutic response we observed was between the genotype we predicted to be least favorable on the basis of previous studies (*CCR5* +/+ | *CCR2*+/+ | *CCR5-59029* A/A) and other genotypes. In an analysis that did not consider the *CCR5-59029* allele, Valdez *et al.* recently reported that HIV-1-infected *CCR5-[DELTA]32* heterozygotes had a more favorable prognosis than did patients who were wild type at that locus [22]. *CCR5-[DELTA]32* heterozygotes tended to have low rates of virologic failure in our study as well, but the finding was not statistically significant. Different study designs and definitions of virologic success may account for the somewhat different findings in these two studies. It should also be noted that our study had relatively low statistical power to detect modest differences among genotypes. A larger study may be needed to fully evaluate the relationship between host genotype and therapeutic response to antiretroviral treatment.

We found no evidence that patients who are homozygous for the *SDF-1 3'A* allele had a more favorable therapeutic response. However, if the *SDF-1 3'A* allele acts late in the course of infection through interaction with the CXCR4 HIV-1 receptor [11], that polymorphism would be unlikely to affect viral suppression in patients with relatively high CD4+ lymphocyte counts such

as the ACTG 343 study population. We did not examine some other genetic polymorphisms that have been associated with differences in HIV natural history, such as additional CCR5 promoter polymorphisms [10] or HLA haplotype [23]. Incorporation of additional genetic markers into the analysis will require a study with a larger sample size.

Factors shown to influence the likelihood of viral suppression in previous studies include baseline HIV RNA level, baseline CD4+ lymphocyte count, and adherence to therapy [24]. Our results suggest that host genotype may also alter therapeutic response to antiretroviral regimens. If validated, these findings could mark an initial step in the integration of host genetic information into the treatment of viral infections.

Acknowledgements

We thank Dianne Wang, Chiuchin Yuan and David Waters for performing genotyping, the ACTG 343 protocol team and investigators for their contributions to the study, and the patients for their participation.

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Keywords: AIDS; antiretroviral therapy; CC-chemokine receptor 5; genotype; HIV; HIV RNA; protease inhibitors; treatment response

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Accession Number: 00002030-200005050-00008
